COMMENTARY

Cross-Presentation: For Better or Worse

Anne Hosmalin, M.D., Ph.D., is a Research Director and Professor at the Cochin Institute in Paris, France. She obtained her M.D. from Descartes University in 1986 and her Ph.D. in Immunology from Pierre & Marie Curie University. Her three-year postdoctoral Fogarty fellowship with Jay Berzofsky, M.D., Ph.D., now Chief of CCR's Vaccine Branch, in the early days of HIV vaccine research, kindled interests that still form the basis of her current research agenda. Her work spans basic investigations into the roles of antigen-presenting cells in orchestrating immune responses to the quest for more effective vaccines. She also serves as President of the French Society of Immunology.

When the immune system encounters a new microbe or a nascent tumor, a quick and effective defense is critical to good health; when the same system encounters an allergen or a cell from a developing fetus, tolerance is equally essential. I study dendritic cells because they are at the center of the immune system's decision to mount a defense or promote tolerance. They process antigens from a variety of sources and present them as foe or friend to lymphocytes that carry out the immune response. My laboratory is particularly focused on cross-presentation, whereby dendritic cells present exogenous antigens to cytotoxic T cells (CTLs) to promote their widespread destruction. Understanding and coaxing effective cross-presentation is central to vaccine development. Dendritic cells are a natural immunological adjuvant, but we are still learning how to stimulate them optimally.

From Mice to Man

I first became interested in antigen presentation during my postdoctoral work on HIV. It was a very exciting time in Jay's laboratory, during which we found the first viral epitopes that elicited CTL responses, and that formed the basis of early vaccine attempts. When I went back to France, I decided to move from studying antigen presentation in mice to investigating the properties of human dendritic cells. At the time, very few people were studying them; one had to isolate them with great difficulty from lymphoid organs. Once methods were developed to culture them from monocytes, the dendritic cell field exploded. A great deal has been learned about the mouse dendritic cell system, and how different subpopulations function; however, it has been a challenge to translate much of the work that has been done in mice into humans.

We have learned that populations of dendritic cells in the blood can perform cross-presentation; my laboratory was the first to demonstrate this function for plasmacytoid dendritic cells, which are relatively small cells, known for producing α-interferons in response to viruses. People were initially quite resistant to the idea that these cells were also antigen-presenting cells, but now there are even some tumor vaccine trials in the Netherlands and France that take advantage of these dendritic cells. We were also one of the teams that published four back-to-back *Journal of Experimental Medicine* papers in 2010, which identified a population of CD141+ dendritic cells in human blood that are equivalent to the well-studied mouse CD8+ dendritic cells that specialize in cross-presentation.

> Understanding and coaxing effective cross-presentation is central to vaccine development.

(Photo: Courtesy of A. Hosmalin)

Anne Hosmalin, M.D., Ph.D.

HIV and Hyperactivation

In 1999 we showed that there was a deficiency in the circulating dendritic cells of chronic HIV patients. Recently, we found that there is a subpopulation of nonclassical monocytes—not dendritic cells—expressing M-DC8 that are more numerous and hyperactivated in patients with elevated levels of the HIV virus.

HIV is relatively well controlled in patients from wealthy countries, but patients still suffer from a counterintuitive hyperactivation of the immune system, causing the immune system to age faster than it should and also producing cardiovascular complications whether or not patients are being treated with antiretrovirals. Depletion of CD4+ T cells protecting the gut opens the way for bacterial lipopolysaccharides (LPS) to chronically stimulate an immune response, even in the absence of significant active HIV virus.

When M-DC8+ monocytes are stimulated with LPS, we found that they secrete TNFα, one of the main cytokines responsible for immune hyperactivation. So we hope if we can neutralize this specialized cell population, we can break the vicious cycle of immune hyperactivation that occurs even under antiretroviral therapy. If we succeed in calming the immune system, interruptions of antiretroviral administration might become possible, which would improve quality of life.

Whereas many other countries have stopped or slowed their research on HIV, the French AIDS Research Agency (ANRS), like the NIH, has sustained funding over time, making France one of the strongest contributors to the literature on HIV and retrovirology. The ANRS supports basic research on immunology and virology, as well as research in the social sciences. As industry became disenchanted with the early failures of HIV vaccine research, it has been up to agencies like the NIH and ANRS to solve some of the fundamental challenges limiting our success.

Life at the Cochin Institute

The Cochin is a large institute, jointly supported by Institut national de la santé et de la recherche médicale (INSERM), Centre national de la recherche scientifique (CNRS), and the University Paris Descartes. It comprises 650 people who are divided among 35 teams and technological platforms. In addition to running my own laboratory, I am also Director of the Department of Infection, Immunity, and Inflammation, one of three departments in the Institute. The department comprises 14 teams that work on immunology—from immune cells to diseases such as infections, cancer and autoimmune or inflammatory diseases—and on host interactions with bacteria, parasites, and retroviruses.

If we succeed in calming the immune system, interruptions of antiretroviral administration might become possible, which would improve quality of life.

In France, the Cochin Institute was the first to develop a model in which we could systematically share cutting-edge technological platforms, much as the NIH has core facilities with staff dedicated to maintaining and building on valuable technologies for the benefit of a variety of investigators. In addition, there are many different competencies among the teams, so, for example, we can easily find an expert on cell signaling to share techniques or reagents, even if they are in another department altogether. It is a rich environment for young researchers, which is important to me. On a day-to-day basis, one of the aims in my scientific life—besides those of achieving new treatments or uncovering basic mechanisms of antigen presentation—is to pass along to the next generation of researchers the scientific and ethical values, as well as the mentorship and opportunities that I have received.